Formulation Development and Invitro Assessment of Macrolide Drugs of Microemulgel for Antibacterial Activity

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Introduction

Emulsion and gel are used in a combined form the dosage form prepared is named as Emulgel As the name suggests it is the combination of emulsion and gel In fact, the presence of a gelling agent in water phase converts an ancient emulsion into emulgel

The direct (oil-in-water) system is used to entrap lipophilic drugs, while hydrophilic drugs are encapsulated in the reverse (water-in-oil) system Emulsions have a certain degree of elegance and are easily washable. They also have a high ability to penetrate the. Topically used emulgels have several desirable properties like being thixotropic, greaseless, easily spreadable as well as removable, emollient, non-staining, water soluble, longer shelf-life, bio-friendly, transparent, pleasant etc

- When both micro-emulsion and gel are used in combination dosage forms the prepared formulations are called as microemulgel, having the advantages of both emulgel as well as micro-emulsion. Both hydrophilic and hydrophobic types of drugs are incorporated into dosage forms. They provide a large surface area for drug absorption and oil portion increases the bioavailability by improving permeability of drugs. Also, the stability of micro-emulsion is increased when it is incorporated in gel. Over to micro-emulsions, microemulgels have a certain degree of elegance and easily washable whenever required
- Microemulsion is a isotropic mixture of oil, surfactant and co-surfactant and drug. Microemulsion have been successfully used to improve the solubility chemical stability and oral bioavailability of many poorly water-soluble drugs. Microemulsion is homogenous transparent thermodynamically stable dispersion of water and oil stabilized by a surfactant usually in combination with a co-surfactant
- Microemulsion might defined as are liquid dispersion of water and oil that are made homogenous stable solution
- When both microemulsion and gel are used in combination dosage form the prepared formulation are called as microemulgel

Advantages of Emulgel

- Hydrophobic drug can be easily incorporated by using o/w emulsion.
- Better stability.
- Better loading capacity.
- Low preparation cost.
- Prolonged effect of drug (controlled release).
- Improve patient compliance.
- Avoidance of first pass metabolism.
- Self-applied medication.

- Termination of therapy when required.
- Suitable for drug with short half-life and for potent drug.
- Site specific drug delivery system
- Avoidance of gastrointestinal incompatibility

Emulgel emerges as one of the important and better way of delivering the drug; it is because of its better control ability over the other topical dosage forms. Many widely used topical agents like ointment, cream and lotion have many disadvantages i.e. very sticky causing uneasiness to the patient when applied. They have lesser spreading coefficient and need to apply with rubbing and they exhibit the stability problem. Due to all these factors within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparations. A gel is colloid that is typically 99% weight liquid, which is immobilized by surface tension between it and a macromolecular network of fibers built from a small amount of gelatin substance present. In spite of many advantages a major limitation is in delivery of hydrophobic drugs. So to overcome this limitation an emulsion based approach is being used so that a hydrophobic therapeutic moiety can be successfully incorporated and delivered through gels. The Emulgel preparations are much more stable than that of other types of topical preparation like powder may be hygroscopic that may absorb environmental humidity during its direct exposure to the surroundings, creams shows phase inversion and the ointment shows rancidity due to oil base.

Mostly drugs are very much effective by oral and/or parenteral routes but have drawbacks of unwanted side effects, so the requirement of alternate routes of administration like topical, ophthalmic, vaginal etc. Mostly drugs are poorly water soluble, so have the problem of penetrating through the skin. Selection of oil, emulsifiers and co-emulsifiers for preparation are based on solubility of it in them, so the problem of solubility would be overcome. Oil portion has more or less pharmacological action and itself enhances penetration. Microemulgel enhances deposition of drug moieties at the site, so therapeutic activity is also increased. Stability is more as compared to micro-emulsion.

Macrolides are a class of antibiotics derived from *Saccharopolyspora erythraea* (originally called *Streptomyces erythreus*), a type of soil-borne bacteria.

Macrolides inhibit protein synthesis in bacteria by reversibly binding to the P site of the 50S unit of the ribosome. Macrolides mainly affect gram-positive cocci and intracellular pathogens such as mycoplasma, chlamydia, and legionella. Erythromycin was the first macrolide discovered; other macrolides include azithromycin, clarithromycin, and roxithromycin.

Their action is primarily bacteriostatic but may be bactericidal at high concentrations, or depending on the type of microorganism.

Macrolides are the first choice of antibiotics to treat pneumonia, chlamydia, and urethritis. These antimicrobials are also known to have immunomodulatory benefits and anti-inflammatory properties, so they can treat other conditions rather than just bacteria infections. Common examples would be their use for cystic fibrosis and chronic obstructive pulmonary disease (COPD) symptoms

Macrolide antimicrobial agents are a type of antibiotic that consists of at least one macrocyclic lactone ring, which makes its pharmacology capable of having either antifungal or antibacterial properties. The macrolide antibiotic mechanism of action involves stopping the RNA that is responsible for bacterial protein synthesis and therefore, suppressing the bacteria's growth. RNA is able to be altered by macrolides reversibly binding to something called the P site on the 50S ribosomal subunit found in microorganisms such as bacteria. This prevents the production of protein in certain bacteria that is required for them to thrive.

STUDY OBJECTIIVE

Aim: Formulation, Development and Evaluation of Microemulgel.

Objective

- Prepared and optimized micro-emulsion from selected oil with emulsifier and co-emulsifier in which an API has the maximum solubility.
- Optimized formula of microemulgel with different grades and different concentrations of the gelling agent by applying suitable statistical design.
- To evaluate the combined effect of oil and API and compare it to API alone and available marketed preparation.

Rationale of study

- Microemulgel could bring about dual control release system i.e. gel and micro-emulsion with an increase in the pharmacological activity at the site of action and reduction in side effects with advantages of emulgel.
- Oil probably is having more or less pharmacological property, surfactant and co-surfactant one from each category will be screened on the basis of solubility studies of API(s) in it, so the problem of solubility of API will be overcome.
- Microemulgel formulation enhances the skin deposition of API, thereby presumably enhancing its therapeutic activity.

LITERATURE REVIEW

- **Kern (2015)-** After some years of stagnation there have been several new successful developments in the field of antibacterial agents. Most of these new developments have been in conventional antibacterial classes. New drugs among the beta-lactam agents are methicillin-resistant Staphylococcus aureus (MRSA) active cephalosporins (ceftaroline and ceftobiprole) and new combinations of beta-lactam with beta-lactamase inhibitors (ceftolozane/tazobactam, ceftazidime/avibactam, imipenem/relebactam and meropenem/RPX7009). New developments can also be observed among oxazolidinones (tedizolid, radezolid, cadazolid and MRX-I), macrolides/ketolides (modithromycin and solithromycin), aminoglycosides (plazomicin), quinolones (nemonoxacin, delafloxacin and avarofloxacin), tetracyclines (omadacycline and eravacycline) as well as among glycopeptides and lipopeptides (oritavancin, telavancin, dalbavancin and surotomycin). New agents in a very early developmental phase are FabI inhibitors, endolysines, peptidomimetics, lipid A inhibitors, methionyl-tRNA synthetase inhibitors and teixobactin.
- **Porter (2016)-** Exacerbations of asthma and COPD are triggered by rhinoviruses. Uncontrolled inflammatory pathways, pathogenic bacterial burden and impaired antiviral immunity are thought to be important factors in disease severity and duration. Macrolides including azithromycin are often used to treat the above diseases, but exhibit variable levels of efficacy. Inhaled corticosteroids are also readily used in treatment, but may lack specificity. Ideally, new treatment alternatives should suppress unwanted inflammation, but spare beneficial antiviral immunity. In the present study, we screened 225 novel macrolides and tested them for enhanced antiviral activity against rhinovirus, as well as anti-inflammatory activity and activity against Gram-positive and Gram-negative bacteria. Primary bronchial epithelial cells were grown from 10 asthmatic individuals and the effects of macrolides on rhinovirus replication were also examined
- **Cui.w; ma (2011)-** The continuing emergence of bacterial resistance has provided an incentive for recent intensified research on macrolide antibiotics. Belonging to the macrolide family, 16-membered macrolides also experience a renewed interest in further exploration. The medicinal potential of 16-membered macrolides in search for new antibacterial stems from some advantages over 14-membered macrolides, such as gastrointestinal tolerability, structural flexibility, and lack of inducible resistance. Thus, compared with abundant articles on various 14-membered macrolide derivatives in the literature, this review will highlight some representative 16-membered macrolide antibiotics and their recently discovered analogs. Furthermore, the action and resistance mechanisms of 16-membered macrolide antibiotics will be elucidated as well to assist the drug design
- **Palejktahana(2017)-** Macrolides, polyketide natural products, and their 15-membered semi-synthetic derivatives are composed of substituted macrocyclic lactone ring and used primarily as potent antibiotics. Recently their usefulness was extended to antimalarial and anti-inflammatory area. Hybrid macrolides presented in this article are the next generation semi-synthetic compounds that combine pharmacophores from antibacterial, antimalarial and anti-inflammatory area with 14- and 15-membered azalide scaffolds. Antibacterial azalide hybrids with sulphonamides showed improved activity against resistant streptococci while quinolone conjugates demonstrated full coverage of respiratory pathogens including macrolide resistant strains and their efficacy was confirmed in mouse pneumonia model. Antimalarial macrolide hybrids, mainly involving (chloro)quinoline pharmacophores, showed

outstanding activity against chloroquine resistant strains, favourable pharmacokinetics, promising in vivo efficacy as well as encouraging developmental potential. Anti-inflammatory hybrids were obtained by combining macrolides with corticosteroid and non-steroidal anti-inflammatory drugs. They were found active in in vivo animal models of locally induced inflammation, asthma, inflammatory bowel disease and rheumatoid arthritis and demonstrated improved safety over parent steroid drugs. Overall, macrolide hybrids possess significant potential to be developed as potent novel medicines in therapeutic areas of utmost pharmaceutical interest.

- **Emmet(2015)-** Community-acquired pneumonia (CAP) is a leading cause of death from an infectious cause worldwide. Guideline-concordant antibiotic therapy initiated in a timely manner is associated with improved treatment responses and patient outcomes. In the post-antibiotic era, much of the morbidity and mortality of CAP is as a result of the interaction between bacterial virulence factors and host immune responses. In patients with severe CAP, or who are critically ill, there is a lot of emerging observational evidence demonstrating improved survival rates when treatment using combination therapy with a Î²-lactam and a macrolide is initiated, as compared to other antibiotic regimes without a macrolide. Macrolides in combination with a Î²-lactam antibiotic provide broader coverage for the atypical organisms implicated in CAP, and may contribute to antibacterial synergism.
- **Padovan(2016)** As we face an alarming increase in bacterial resistance to current antibacterial chemotherapeutics, expanding the available therapeutic arsenal in the fight against resistant bacterial pathogens causing respiratory tract infections is of high importance. The antibacterial potency of macrolones, a novel class of macrolide antibiotics, against key respiratory pathogens was evaluated in vitro and in vivo MIC values against Streptococcus pneumoniae, Streptococcus pyogenes, Staphylococcus aureus, and Haemophilus influenzae strains sensitive to macrolide antibiotics and with defined macrolide resistance mechanisms were determined. The propensity of macrolones to induce the expression of inducible erm genes was tested by the triple-disk method and incubation in the presence of subinhibitory concentrations of compounds. In vivo efficacy was assessed in a murine model of S. pneumoniae-induced pneumonia, and pharmacokinetic (PK) profiles in mice were determined. The in vitro antibacterial profiles of macrolones were superior to those of marketed macrolide antibiotics, including the ketolide telithromycin, and the compounds did not induce the expression of inducible erm genes. They acted as typical protein synthesis inhibitors in an Escherichia coli transcription/translation assay. Macrolones were characterized by low to moderate systemic clearance, a large volume of distribution, a long half-life, and low oral bioavailability. They were highly efficacious in a murine model of pneumonia after intraperitoneal application even against an S. pneumoniae strain with constitutive resistance to macrolide-lincosamide-streptogramin B antibiotics
- **Neu H; C (2011)-** Macrolide antibiotics have been available and used clinically since 1952. The class of drugs originated from a soil sample obtained from the City of Ilo-Ilo on the Island of Paray in the Philippines. Erythromycin has been the most widely used agent of this class called 'macrolides' because they possess the macrocyclic lactone nucleus. Many esters of erythromycin are well established as agents to treat a variety of respiratory and cutaneous infections, particularly in children. There has been a resurgence of interest in macrolides as a result of the recognition of pathogens such as Legionella, Chlamydia and Campylobacter spp. A number of new 14-membered macrolides have been synthesised in recent years with the goal

of overcoming some of the problems of the older erythromycin agents. There has been variable activity of erythromycin against Haemophilus influenzae

- **Zedan(2012)-** Long-term therapy with the macrolide antibiotic erythromycin was shown to alter the clinical course of diffuse panbronchiolitis in the late 1980s. Since that time, macrolides have been found to have a large number of anti-inflammatory properties in addition to being antimicrobials. These observations provided the rationale for many studies performed to assess the usefulness of macrolides in other inflammatory diseases including skin and hair disorders, such as rosacea, psoriasis, pityriasis rosea, alopecia areata, bullous pemphigoid, and pityriasis lichenoides. This paper summarizes a collection of clinical studies and case reports dealing with the potential benefits of macrolides antibiotics in the treatment of selected dermatoses which have primarily been classified as noninfectious and demonstrating their potential for being disease-modifying agents
- **Jasna(2016)-** Clarithromycin has increased activity against Legionella, and Branham Ella spp., and Pasteurella multocida, and, with its 14-OH metabolite, inhibits Haemophilus spp. It is also more active against chlamydia and against anaerobic species while retaining excellent activity against streptococci including Streptococcus pneumoniae. It has increased plasma peak levels and a sufficiently long half-life for twice daily administration. Furthermore, it is well tolerated. Thus clarithromycin offers potential for use in those areas in which a safe, well tolerated macrolide will be used, namely respiratory, skin structure and selected diarrhoeal and genital infections.
- **Xu Dong(2016)-** Development of efficient antibacterial agents is critical for human health. In the present study, we investigated the antibacterial activity of polyethyleneimine (PEI)-capped silver nanoclusters (PEI-AgNCs), based on the fact that nanoclusters normally have higher surface-to-volume ratios than traditional nanomaterials and PEI itself has a strong antimicrobial capacity. We synthesized stable silver nanoclusters by altering PEI molecular weight from 0.6 kDa to 25 kDa and characterized them by UV-Vis absorption and fluorescence spectroscopy and high resolution transmission electron microscopy. The sizes of AgNCs were around 2 nm in diameter and were little influenced by the molecular weight of PEIs. The antibacterial abilities of the four PEI-AgNCs were explored on agar plate and in liquid systems. Our results revealed that the antibacterial activity of PEI-AgNCs is excellent and the reduction of PEI molecular weight could result in the increased antibacterial capacity of PEI-AgNCs. Such proposed new materials might be useful as efficient antibacterial agents in practical clinical applications
- **Kusu(2017)-** There is growing evidence for anti-inflammatory activities of macrolides in chronic respiratory diseases, such as diffuse panbronchiolitis, cystic fibrosis, or chronic bronchitis. The long-term effect of macrolides in idiopathic pulmonary fibrosis (IPF) is unknown. This study was aimed to investigate the effect of macrolide therapy on the frequency of acute exacerbation (AE) and the mortality in IPF. A total 52 IPF patients who were treated by combination of conventional agents with or without macrolides were retrospectively reviewed. The primary endpoint was the incidence of AE in IPF patients. We also observed survival rate after the treatment with or without macrolides.
- **Gemma(2018)-** AE was observed in 4 of 29 cases (13.8%) treated with macrolides and 8 of 23 cases (34.8%) treated without macrolides, respectively during 36 months. AE free survival rate of macrolide group was significantly better than that of non-macrolide group (logrank p=0.027). Survival rate of IPF patients with macrolide therapy was significantly better than that of patients without macrolide therapy (p=0.047). Our results indicate the potential

beneficial efficacy of macrolide therapy combined with oral corticosteroids, immunosuppressive or anti-fibrotic agents in IPF

- Qiu, Shilin; Zhong, Xiaoning (2016)- Chronic inflammation plays a central role in the pathogenesis of chronic obstructive pulmonary disease (COPD). However, there are no effective anti-inflammatory pharmacologic therapies available for COPD so far. Recent evidence suggests that an immunologic mechanism has a role in the pathogenesis of COPD. Macrolides possess anti-inflammatory and immune-modulating effects may be helpful in the treatment of COPD. However, the subgroups that most effectively respond to long-term treatment of macrolides still need to be determined. The potential adverse events to individuals and the microbial resistance in community populations raises great concern on the long-term use of macrolides.
- **Takahashi, Shunji (2017)-** Antimicrobial agents are used for the accurate diagnosis of infectious diseases and effective implementation of antibacterial chemotherapy. The role of microbiological technologists is to provide data from microorganism tests useful for rapid infection treatment. Gram strain can be used to observe microorganisms and neutrophils from specimens of a patient. It is also possible to estimate the kinds of microorganism. If bacterial infectious disease is negative, there is no need for antibacterial chemotherapy. The applied dose of antibacterial agents is different in every hospital. Also, there is a difference in the percentage antibacterial agent susceptibility of isolates. Antibiograms must be created to investigate local factors. For empiric therapy, antibiograms are useful when choosing antibacterial agents showing marked efficacy against the clinical isolate. Microorganism test systems which are useful for the proper use of antibacterial agents are necessary to facilitate safe antibacterial chemotherapy and prevent the development of resistant bacteria
- **Stele Helen(2012)-** Macrolide antibiotics possess several, beneficial, secondary properties which complement their primary antimicrobial activity. In addition to high levels of tissue penetration, which may counteract seemingly macrolide-resistant bacterial pathogens, these agents also possess anti-inflammatory properties, unrelated to their primary antimicrobial activity. Macrolides target cells of both the innate and adaptive immune systems, as well as structural cells, and are beneficial in controlling harmful inflammatory responses during acute and chronic bacterial infection. These secondary anti-inflammatory activities of macrolides appear to be particularly effective in attenuating neutrophil-mediated inflammation. This, in turn, may contribute to the usefulness of these agents in the treatment of acute and chronic inflammatory disorders of both microbial and nonmicrobial origin, predominantly of the airways
- **Kegde(2020)-** topical drug delivery is the delivery of drugs anywhere in the body through skin, vaginal, ophthalmic and rectal routes. Drugs may be given for localized or systemic effects. Topical formulations with varying physicochemical properties, such as solid, semisolid, or liquid, can be developed. The topical system is created by preparing a drug emulsion and incorporating it into an emulgel. Emulgel is a thermodynamically stable formulation with low interfacial tension that is made by combining a surfactant and a co-surfactant and has several properties such as increased permeability and good thermodynamic stability. Emulgel has a dual control and a sustained release pattern. Emulgel improves bioavailability as well as patient compliance. The pH, viscosity, particle size, zeta potential, drug content, stability study, skin irritation test, and other properties of the prepared formulation are evaluated

- **J.P Singh(2019)-** Topical drug delivery is mostly preferred for dermatological action. Topical dosage form such as cream, ointments, gels etc. has certain drawbacks like stability problems, stickiness, poor absorption as well as permeability. It has limitations in terms of drug solubility, residence time, lipophilicity and permeability. To overcome this, a novel approach microemulsion based gel is formulated. Microemulgel is topical drug delivery system that incorporates the properties of both gel and microemulsion and shows dual release control system. The microemulgel is prepared by reducing the globule size of the emulsion (less than 200nm) so that the drug particles can easily penetrate through stratum corneum.

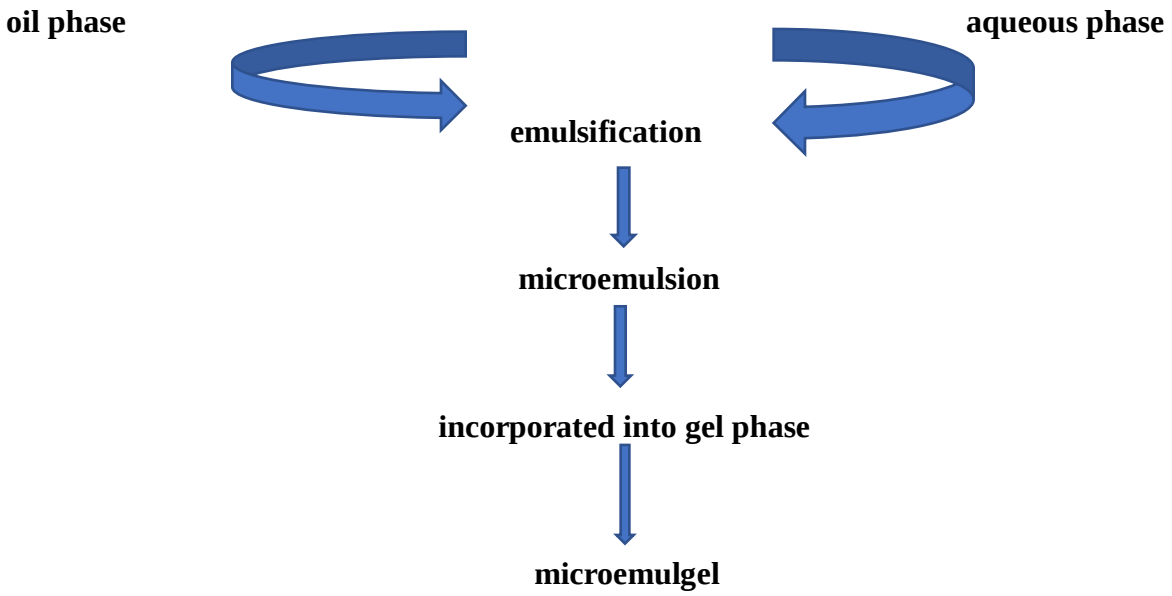
- **Rode. R.J (2021)-** Emulgel is a new approach and recent technology of NDDS for topical drug transport having characteristics of dual controlled release i.e emulsion and gel Emulsion used for treating for muscle pain, headache, acne, psoriasis, rheumatoid arthritis. When emulsion and gel used in combination its known as Emulgel. Emulgel is transparent gel which is used in pharmaceutical and cosmetic product. Emulgel overcome the problem which is come in gel and emulsion. Gel is a new class of formulation, gel release drug faster in comparison of ointment, cream, lotion etc. Limitation of gel in the delivery of hydrophobic drug through the skin. Overcome the limitation on emulsion based approach is being used so that even a hydrophobic therapeutic moiety can exhibit the unique properties of gels. Emulgel is prepared by different polymers which act as an emulsifying agent and thickening agent because the gelling capacity of these polymers give rise to stable emulsions by decreasing interfacial and surface tension while at the same time increasing the viscosity of the aqueous phase. Emulgel are having major advantages on novel vesicular systems as well as on conventional systems considering various aspects. The emulgel provide several favourable properties for its dermatological use such as greaseless, thixotropic, easily spreadable, emollient, easily removable, non-staining, water soluble, longer shelf life, transparent, bio-friendly and pleasing appearance

RESEARCH METHODOLOGY

Important constituents for the preparation of Emulgel

- Vehicle
- Aqueous material
- Oils Emulsifiers Gelling Agents Permeation enhancers

Step1: Formation of emulsion either o/w or w/o.
Step2: Formation of gel base.
Step3: Incorporation of emulsion into gel base with continuous stirring



Vehicle

The vehicle is an important link between drug potency and therapeutic effectiveness, since extensive pharmaceutical research has shown that the composition of vehicle can profoundly influence the rate and extent of absorption. Substance in the vehicles, such as humectants, which have high affinity for water, may under certain circumstances dehydrate the stratum corneum and decrease penetration. They also affect the penetration of drug by loss of water vapor on the skin surface

The vehicle has following properties:

- Deposit the drug on the skin with distribution.

- The release of drug migrates freely at the site of action.

- Deliver the drug at the target site and sustain the drug release.

- Appropriately formulated for the anatomic site to be treated.

- Cosmetically acceptable to the patent. Aqueous material Aqueous material forms the aqueous phase of emulsion. The commonly used agents are water and alcohols etc

Oils form the oily phase of the emulsion. For externally applied emulsion, non-biodegradable mineral castor oils that provide a local laxative effect, fish liver oils or various fixed oils of vegetable origin as nutritional supplement

Emulsifier

Emulsifying agent is mainly used for the promotion of emulsification of oil and aqueous phase at the time of formulation. They retard the phase separation of emulsion by increasing the stability and shelf life of emulsion can be vary from days to months or years for commercial preparation. Emulgel mostly contains Polyethylene glycol, Sorbitan mono-oleate (Span 80), Polyoxyethylene sorbitan monooleate (Tween 80), Stearic acid and sodium stearate as emulsifying agents

Gelling agents

These agents are used to form gel base to incorporate emulsion in it to prepare Emulgel. Gelling agents are used to increase the consistency of any dosage form by swelling in aqueous phase and form gel like structure. These are used as thickening agent in Emulgel.

ACTIVITY PLAN

1st semester

- Finalize topic & searching literature - 6 months
- Synopsis Preparation - 3 month

2nd sem and 3rd sem

- Procurement &authentication of drug and collection of excipients &extensive researchwork submission of at least research paper in journal of repute - 10 months

4th semester

- Compilation of data - 3 months
- Writing of thesis work - 2 months
- Submission of thesis - 1 month

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